Process for Preparation of the Report on Carcinogens

The Report on Carcinogens (RoC) is a Congressionally mandated, biennial document that identifies and discusses agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") that may pose a hazard to human health by virtue of their carcinogenicity. Substances are listed in the report as either *known* or *reasonably anticipated to be human carcinogens*, and a description of the substance, its uses, potential sources of exposure, the rationale for listing, and applicable federal regulations are included in the RoC in a "substance profile." Each edition of the report is cumulative. The National Toxicology Program (NTP) prepares the RoC on behalf of the Secretary of Health and Human Services (HHS). Review of candidate substances and preparation of the report are managed by the Office of the Report on Carcinogens (ORoC) within the Division of the NTP, National Institute of Environmental Health Sciences (NIEHS).

A schematic of the process for preparation of the RoC is provided below. The process has four parts: (1) nomination and selection of candidate substances, (2) scientific evaluation of candidate substances, (3) public release and peer review of draft RoC monographs, and (4) HHS approval and release of the latest edition of the RoC. Each part is described below.

Nomination and Selection of Candidate Substances

The NTP invites nominations of substances for consideration for listing in the RoC from anyone in the public or private sector. A nomination may seek to list a new substance in the RoC, reclassify the listing status of a substance already listed, or remove a substance already listed. Nominations may be submitted by mail or fax to ORoC[1] or online at http://ntp.niehs.nih.gov/go/27911.

A nomination should contain a rationale or reason for the RoC review and, if possible, appropriate background information and relevant data to support the rationale (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer Monographs, exposure surveys, or release inventories).

ORoC initially evaluates each nomination to determine whether there is sufficient information on exposure and carcinogenicity to justify formal evaluation of the substance and its consideration for the RoC. ORoC informs its partner agencies of nominations and invites their review.[2] The NTP solicits public comments on nominations through the *Federal Register,* requesting information about ongoing studies, recent publications, current production, use patterns, sources of exposure, and the names of scientific experts with relevant knowledge, as well as scientific issues important for assessing the carcinogenicity of the substance. Public comments received on the nominations are posted on the RoC website (http://ntp.niehs.nih.gov/go/roc). The NTP considers the interagency and public comments and identifies nominated substances for evaluation for the RoC. Those nominated substances proposed for evaluation are evaluated

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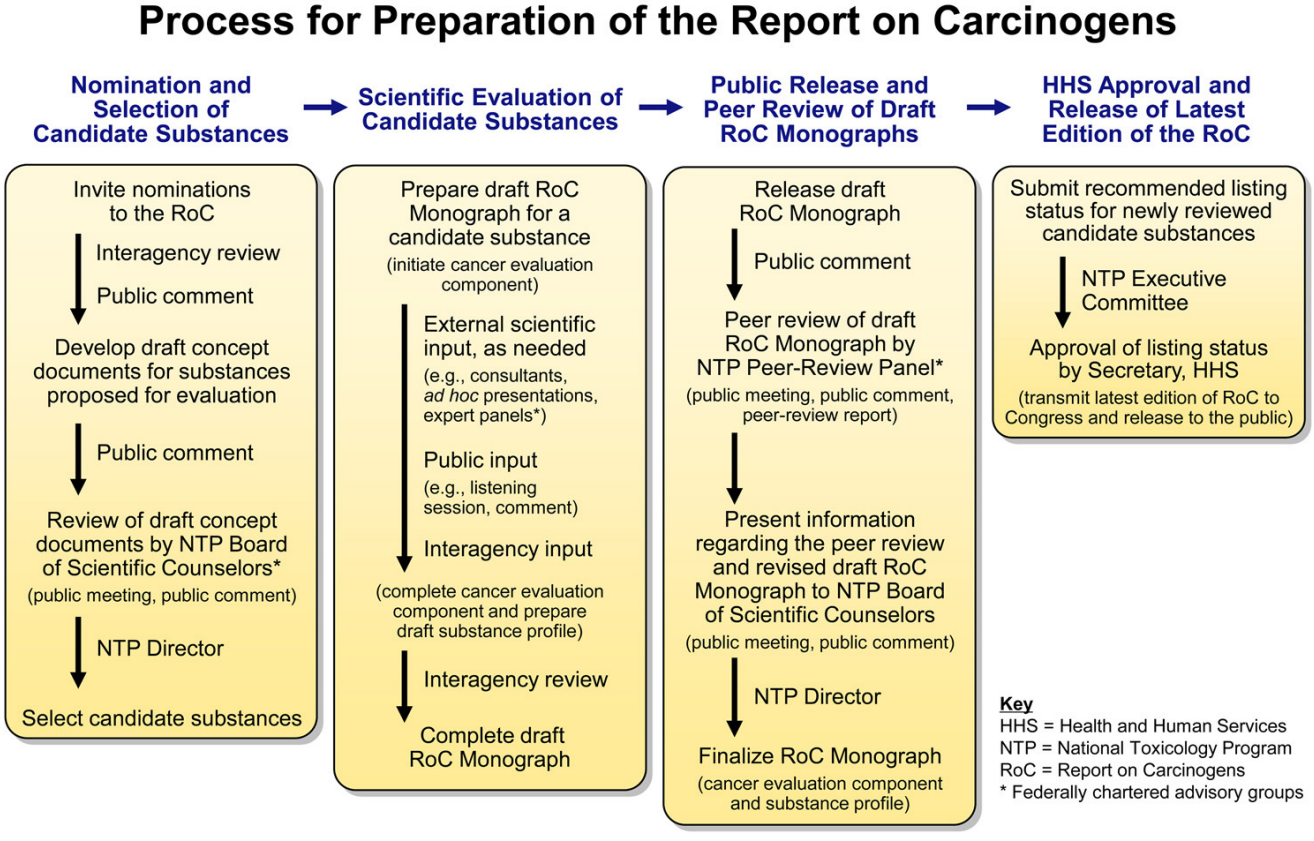
[2]Interagency review is invited from agencies represented on the NTP Executive Committee, including the Consumer Product Safety Commission, Department of Defense, Environmental Protection Agency, Food and Drug Administration, National Cancer Institute, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health, and Occupational Safety and Health Administration.



by the process described below. For those nominated substances not selected for evaluation, the NTP notifies the nominators.

For each substance proposed for evaluation, ORoC prepares a draft concept document. The concept document is a brief document that outlines the rationale for the nomination of the substance, including information on exposure, the extent and nature of the scientific evidence for evaluating carcinogenicity in humans and experimental animals, and any major relevant issues, such as proposed mechanisms or modes of action of carcinogenicity. The concept document also lays out the proposed approach to development of the cancer evaluation component of the draft RoC Monograph on the substance, including the search strategy for identifying relevant scientific literature and the strategy for obtaining external scientific and public input (see Scientific Evaluation of Candidate Substances). The NTP announces one or more proposed substances for evaluation and solicits public comments on draft concept documents through announcements in the *Federal Register* and NTP publications.

The NTP presents the draft concept document for a substance to the NTP Board of Scientific Counselors (BSC)[3] at a public meeting that provides opportunity for public comment.[4] The BSC is asked to comment on the draft concept document for a proposed substance, including (1) the rationale for its review for the RoC and (2) the proposed approach for obtaining external scientific and public input in development of the cancer evaluation component of its draft RoC Monograph. The NTP considers the BSC comments and public comments, and the NTP Director makes the final determination whether to add the substance to the list of candidate substances for RoC evaluation. Concept documents for approved candidate substances are finalized based upon BSC comments and public comments and posted on the NTP RoC website (http://ntp.niehs.nih.gov/go/roc). The NTP maintains the complete list of candidate substances on the NTP RoC website. The list includes all substances for which concept documents have been approved for review, but placement on this list does not necessarily mean that the substance will undergo review for any specific edition of the RoC. The NTP may defer or terminate the review of a candidate substance for the RoC at any time if relevant information becomes available that warrants its reconsideration or if scheduling issues preclude completion of a timely review. In such cases, the nominator, the BSC, the NTP Executive Committee, and the public are notified of this action.

Scientific Evaluation of Candidate Substances

ORoC prepares a draft RoC Monograph for each candidate substance. The RoC Monograph has two parts: (1) a cancer evaluation component that reviews all information that may bear on a listing decision, assesses its quality and sufficiency for reaching a listing decision, applies the RoC listing criteria[5] to the relevant scientific information, and recommends an RoC listing status for the candidate substance and (2) a substance profile that contains the NTP's preliminary listing recommendation and a summary of the scientific evidence considered key to reaching that recommendation.

In general, the cancer evaluation component addresses the following topics, although other topics may be included when relevant to evaluating the carcinogenicity of the candidate substance:

- properties (e.g., chemical, physical, or biological), production, and use
- human exposure
- toxicokinetics[6]
- cancer studies in humans
- cancer studies in experimental animals
- mechanisms of cancer induction and other related effects

Information on exposure and properties of the candidate substance must come from publicly available sources, and all scientific information used to evaluate the potential carcinogenicity of a candidate substance must come from peer-reviewed, publicly available sources.

The cancer evaluation component of the RoC Monograph (1) presents the literature search strategy and the literature inclusion/exclusion criteria, (2) identifies and describes the studies relevant for the RoC evaluation, (3) assesses the quality of individual studies and discusses their usefulness for informing the evaluation of carcinogenicity, (4) assesses the level of evidence from human studies or experimental animal studies in applying the RoC listing criteria, and (5) integrates the overall body of evidence (human, animal, and mechanistic) and reaches a preliminary RoC listing recommendation for the substance.

The nature, extent, and complexity of the scientific information on a candidate substance guides the approach used by the NTP to develop the cancer evaluation component. The approach is tailored to enable ORoC to obtain external advice and address scientific issues in assessing the carcinogenicity of a given candidate substance, and the approach may differ among substances. The approach may include external scientific input (e.g., expert panel,[7] *ad hoc* presentations, or individual technical advisors or consultants), public input (e.g., listening session or comments), and/or interagency input. All public comments received during the evaluation become part of the public record, are posted on the RoC website, and are considered by the NTP and any external advisors during subsequent steps in the evaluation process.

ORoC completes the draft cancer evaluation component with consideration of all inputs to its development. Based on the draft cancer evaluation component, ORoC prepares the draft substance profile. These two documents are compiled to form the draft RoC Monograph.

The NTP requests comment on the draft RoC Monograph from its partner agencies, considers this input, and completes the draft monograph.

Public Release of Draft RoC Monograph and Peer Review

The NTP releases the draft RoC Monograph for public comment and then convenes a meeting of an external scientific panel[7] for peer review of the draft RoC Monograph. Prior to the meeting, the NTP publishes a *Federal Register* notice announcing the peer review and the availability of the draft RoC Monograph and inviting written public comment. The public is also invited to attend the meeting and provide oral comments.

[3]The BSC is a federally chartered advisory committee whose members are appointed by the Secretary of HHS. The BSC provides advice to the NTP Director on matters relating to scientific program content and evaluates the scientific merit of the NTP's intramural and collaborative programs; http://ntp.niehs.nih.gov/go/164.

[4]NTP practice is to allot seven minutes per speaker, one speaker per organization, for presentation of oral public comments.

[5]RoC listing criteria are the standards against which the scientific evidence for carcinogenicity is evaluated to determine whether a candidate substance should be listed in the RoC and, if so, whether as *known to be a human carcinogen* or *reasonably anticipated to be a human carcinogen*. The criteria are available at http://ntp.niehs.nih.gov/go/15209.

[6]Toxicokinetics describes the rate at which a chemical enters the body and how it is handled within the body.

[7]NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge selected by the NTP from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with the Federal Advisory Committee Act and HHS implementing guidelines; http://ntp.niehs.nih.gov/go/166.

The NTP sets aside time at the meeting for discussion of scientific issues raised in the public comments. The peer-review charge is twofold: (1) to comment on the cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria, and (2) to comment on the substance profile, specifically, whether the scientific justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of the candidate substance. The panel votes on (1) whether the scientific evidence supports the NTP's level of evidence for human studies or experimental animal studies and (2) whether the scientific evidence supports the NTP's preliminary listing decision. A report of the deliberations by the peer-review panel is prepared and posted on the RoC website.

ORoC considers the peer-review report, prepares the NTP's response to the peer-review report, and posts the response on the RoC website. Based upon the peer-review comments, ORoC prepares a revised draft RoC Monograph. At a public meeting, the NTP provides the BSC with information regarding the peer review. Following the meeting, ORoC, in concert with the NTP Director, finalizes the RoC Monograph on the candidate substance, including the cancer evaluation component and substance profile, and posts the final monograph on the RoC website.

HHS Approval and Release of Latest Edition of the RoC

The NTP submits newly reviewed candidate substances with recommended listing status to the NTP Executive Committee[8] for consultation and then to the Secretary of HHS for review and approval. Upon their approval by the Secretary, the next edition of the RoC is prepared in electronic format, transmitted to Congress, and published on the RoC website for the public. Periodically, the NTP will publish the RoC in both printed and electronic formats, depending upon demand for the printed version.

The NTP publishes a notice in the *Federal Register* and NTP publications announcing the listing outcome for each candidate substance that underwent formal review for the RoC and the availability of the next edition of the RoC.

[8]The NTP Executive Committee is composed of the heads (or their designees) of the federal agencies listed in footnote 2 and provides advice to the NTP on policy issues; http://ntp.niehs.nih.gov/go/163.